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A double-blind, placebo controlled, cross-over comparison of the analgesic effect of ibuprofen 400 mg and 800 mg on laser-induced pain

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1 The analgesic efficacy of single oral doses (400 mg, 800 mg) of ibuprofen on argon laser-induced pain was studied in a double-blind, placebo controlled, three way cross-over comparison. Ten healthy volunteers participated.
2 Pain thresholds and plasma concentrations of the S- and R-enantiomers of ibuprofen were measured every hour up to 8 h after medication.
3 Ibuprofen (400 mg) produced an analgesic effect significantly superior ($P < 0.05$) to placebo 1–4 h after medication. Ibuprofen (800 mg) was significantly superior to placebo 2–4 h after administration. No differences were found between 400 mg and 800 mg, when hourly threshold differences were compared.
4 Comparing total analgesic effect (area under effect curve), both active medications were superior to placebo ($P < 0.01$–0.05), and 400 mg was superior to 800 mg ($P < 0.05$).
5 Peak plasma concentrations of S- and R-ibuprofen occurred between 1.2 and 1.5 h. Concentrations after the 800 mg dose were higher than those after the 400 mg dose at all times.

Keywords ibuprofen analgesia experimental pain plasma concentration laser stimulation

Introduction

Ibuprofen was introduced in 1967, and is widely used as an anti-inflammatory analgesic, especially in rheumatic disorders and for the relief of mild pain (Adams *et al.*, 1969; Beaver, 1988; Kantor, 1979; Miller, 1981). It is more potent than aspirin (Adams *et al.*, 1969, Cooper *et al.*, 1977), and produces fewer gastrointestinal side effects (Kantor, 1979).

In clinical studies ibuprofen was shown to be effective in the relief of pain after dental surgery (Cooper, 1984, 1986; Cooper *et al.*, 1977), pain associated with soft-tissue injuries (Muckle, 1974) and dysmenorrhea (Dawood, 1984), and in the management of post-operative pain (Bloomfield *et al.*, 1974; Iles, 1980) and chronic cancer pain (Stambaugh & Drew, 1988). Analgesic efficacy was evaluated from subjective reports of pain intensity.

A 400 mg dose of ibuprofen has been shown to be more effective than 200 mg (Cooper *et al.*, 1977), but studies using higher doses (Bloomfield *et al.*, 1974; Hopkinson, 1980; Winter *et al.*, 1978) have not demonstrated any dose-related enhancement of analgesia.

The aim of the present study was to compare the analgesic efficacy of ibuprofen 400 mg,

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ibuprofen 800 mg, and placebo over an 8 h period using laser-induced pain as the stimulus. Short argon laser pulses were used to induce a well defined and reproducible pain (Arendt-Nielsen & Bjerring, 1988). To relate the pharmacokinetics of ibuprofen to the analgesic profile, plasma concentrations of the enantiomers of the drug were measured every hour.

Methods

Volunteers

Ten volunteers, five males and five females participated. All subjects were judged to be healthy by medical examination and laboratory tests. Their mean age was 29.7 years (range 21 to 42 years), their mean weight was 66.3 kg (range 57 to 77 kg), and their mean height was 177 cm (range 166 to 186 cm). The study was carried out in accordance with the Declaration of Helsinki and written informed consent was obtained from all of the participants. The study was approved by the Regional Scientific-Ethics Committee, and the National Board of Health.

Medication

Oral doses of ibuprofen 400 mg and 800 mg and placebo were given according to a double-blind randomized three way cross-over design. Each dose comprised two identical appearing tablets. All tablets of active drug contained 400 mg of ibuprofen. The tablets were swallowed with 100 ml of water at 08.00 h on each of the 3 experimental days. The volunteers received all three treatments in random order, and at least 5 days elapsed between subsequent experiments.

The volunteers were fasting from midnight until 3 h after taking the tablets. No other medicine or alcohol was allowed 48 h before and during each experiment.

Laser stimulation and threshold determination

The output from an argon laser (Model 168, Spectra Physics, USA) was transmitted via a quartz fibre to a handpiece. The wavelengths were 0.488 μm (blue) and 0.515 μm (green). Output power could be adjusted from 50 mW to 3.5 W. A continuous low energy beam (50 mW) from the argon laser was directed onto the stimulation site. The laser stimulus had a duration of 200 ms and the laser beam diameter was kept constant at 3 mm by a spacer between the fibre optics and the skin surface. The individual variability in laser pain threshold was previously shown to be 4.3% (Arendt-Nielsen & Bjerring, 1988).

The laser stimulus was applied to the dorsum (C7-dermatome) of the right hand within a target area of 2 × 3 cm^2. Repeated stimulation at identical spots within the area was avoided to exclude the effect of receptor fatigue and receptor sensitization. The intervals between stimuli were random with a mean of 20 s (range 10 to 30 s).

The pain threshold was defined as a distinct pricking pain. The threshold was calculated as a mean of five ascending and five descending series of stimulations (Arendt-Nielsen & Bjerring, 1988). The pain threshold was determined twice before medication and once every hour up to 8 h after ingestion. The volunteers wore goggles to protect their eyes against the laser light and rested comfortably during the measurements.

As a parameter of analgesic efficacy, the pain threshold difference (PTD) was calculated as baseline pain threshold (threshold before medication) subtracted from each hourly pain threshold. Total analgesic effect was calculated as area under the time-efficacy curve (AUEC), using the trapezoidal rule. AUEC values were calculated at 4 and 8 h after medication.

Blood sampling

An i.v. cannula was inserted in the cubital vein in the left forearm, and 10 ml of blood was drawn before drug dosage and at 1, 2, 3, 4, 5, 6, 7, and 8 h after, immediately after determination of the pain threshold. The blood was centrifuged and the plasma was frozen (−20° C) until assay.

Measurement of the R- and S-enantiomers of ibuprofen in plasma

The measurement of the enantiomers was performed according to Pettersson & Olsson (1990). The internal standard 4-pentylphenylacetic acid (Boots Comp. plc Nottingham UK) was added to 0.25–1.0 ml plasma followed by 0.2 ml 3M hydrochloric acid and 6 ml 0.1% (v/v) 2-propanol in *N*-hexane (Lee *et al.*, 1984). After agitation, the samples were centrifuged and the organic layer was transferred to a glass tube and evaporated to dryness. The residue was reconstituted in 0.2 ml 0.01 M phosphate buffer, pH 7.4. The chromatographic system consisted of a LDC ConstaMetric III pump and a Perkin-Elmer ISS-100 autosampler. The u.v. detector was a Spectra 100 (Spectra-Physics, San Jose, CA, USA) operated at 227 nm.

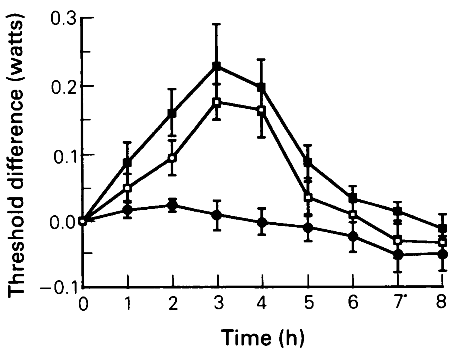

Figure 1 Mean (± s.e. mean) pain threshold difference (watts) following ibuprofen 400 mg (■), ibuprofen 800 mg (□), and placebo (●).

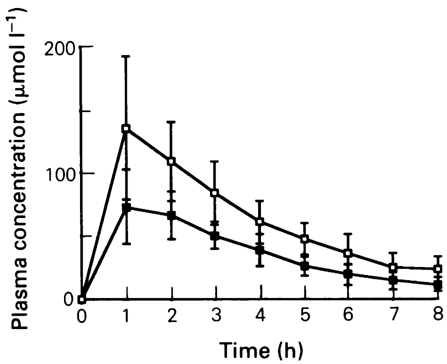

Figure 2 Mean (± s.d.) plasma concentrations (μmol l^{-1}) of S-ibuprofen following administration of racemic ibuprofen 400 mg (■) and 800 mg (□).

Fifty μl was injected onto a 5 μm spherical silica column with immobilized α_1-acid glycoprotein (Chiral-AGP, ChromTech AB, Norsborg, Sweden). The mobile phase (flow rate 1 ml min^{-1}) was 1.2% (v/v) 2-propanol and 1.2 mM dimethyloctylamine in 0.02 M sodium dihydrogen phosphate. The pH of the mobile phase was adjusted with sodium hydroxide to 5.3. The elution order was R- (7 min), S-ibuprofen (9 min), and the internal standard (12 min). The resolution factor (R_s) between R- and S-ibuprofen was 1.2.

Measurements were made using a calibration curve constructed from the assay of five duplicates of standard samples in the range 1–60 μM. The peak area ratios from R- and S-ibuprofen relative to the internal standard were calculated. The limit of assay was 1 μM, at which concentration the relative standard deviation (inter-assay) was 10%.

Intra-assay precision calculated from ten spiked plasma samples, analysed on the same occasion was investigated at three concentrations, 15, 30 and 60 μmol l^{-1}. The coefficient of variation was less than 10% (Pettersson & Olsson, 1990).

Statistical analysis

The two-sided Wilcoxon rank sum test was used and statistical significance was assumed at the 5% level.

Results

The mean time course of pain threshold difference (PTD) following administration of the two ibuprofen doses and placebo is shown in Figure 1.

Ibuprofen (400 mg) had an analgesic efficacy superior to placebo from 1 to 4 h ($P < 0.05$), and marginally superior to placebo ($P = 0.05$) at 5 h. Ibuprofen (800 mg) was found to be superior to placebo ($P < 0.05$) from 2 to 4 h. The efficacy of the 800 mg dose was not different from that of the 400 mg dose. Maximum analgesia was noted at 3 h after administration of both doses (Figure 1).

The total analgesic effect (AUEC) of 400 mg ibuprofen was greater than that of placebo ($P < 0.01$) after 4 and 8 h and exceeded that of ibuprofen 800 mg ($P < 0.05$) after 4 and 8 h. Ibuprofen 800 mg was superior to placebo after 4 ($P < 0.01$) and 8 ($P < 0.05$) h (Table 1).

The concentrations of the pharmacologically active S-enantiomer are shown in Figure 2. They peaked at 1.5 h (mean) following the 400 mg dose, and at 1.4 h following the 800 mg dose. Concentrations after the higher dose were greater than those after the lower dose at all times ($P < 0.004$). Plasma concentrations of R-ibuprofen peaked after 1.5 (400 mg) and 1.2 (800 mg) h and decreased more rapidly and were lower than those of S-ibuprofen.

Following ingestion of 400 mg ibuprofen, five subjects felt tired and one experienced nausea. Administration of 800 mg ibuprofen caused tiredness in three volunteers. No side effects were reported after the placebo tablets.

Discussion

In contrast to clinical findings (Cooper, 1984; Forbes *et al.*, 1984), we observed no analgesia

Table 1 Total analgesic effect following administration of the two ibuprofen doses and placebo, mean (s.d.)

		AUEC (watts × h)	
	Placebo	*400 mg ibuprofen*	*800 mg ibuprofen*
0–4 h	0.05 (0.14)	0.58 (0.36)	0.40 (0.25)
0–8 h	−0.07 (0.37)	0.80 (0.47)	0.48 (0.43)

beyond 4 h. The finding of the 400 mg dosage being significantly superior to the 800 mg ibuprofen, when total analgesic effect was compared, has not been reported in any clinical trials. A possible explanation could be rapid tolerance to the analgesic effect produced by the higher circulating drug concentrations following the 800 mg dose.

Generally, there appears to be an analgesic ceiling effect of NSAIDs; beyond a certain dose, further increments do not yield better analgesia (Beaver, 1988). Several clinical studies have confirmed this view (e.g. Bloomfield *et al.*, 1974; Cooper, 1983; Cooper *et al.*, 1986; Forbes *et al.*, 1982; Hopkinson, 1980; Laska, 1986; Winter *et al.*, 1978).

The time to peak plasma drug concentration found in the present study (1.2–1.5 h) was similar to that reported by others (Albert & Gernaat, 1984; Källström *et al.*, 1988; Müller *et al.*, 1986). The time to peak analgesic effect observed in the present study (3 h) confirms previous clinical findings (Bloomfield *et al.*, 1974; Cooper, 1984, 1986; Cooper *et al.*, 1977; Forbes *et al.*, 1984). Thus, there was a clear delay in the time-course of analgesia relative to the change in plasma drug concentration. Such a delay has also been observed after the administration of other analgesic drugs such as aspirin (Seymour, 1983) and paracetamol (Seymour, 1983).

The analgesic properties of ibuprofen result primarily from the inhibition of prostaglandin cyclo-oxygenase at the site of tissue injury (Doherty *et al.*, 1987; Ferreira *et al.*, 1973; Forbes *et al.*, 1982), thereby preventing the sensitizing activity of prostaglandins at nociceptive nerve endings (Amadio, 1984; Ferreira, 1981; Ferreira & Vane, 1974; Ferreira *et al.*, 1973; Flower *et al.*, 1985).

We find it improbable, that the brief laser pulse of 200 ms used in the present study is sufficient to induce local prostaglandin release and hence be responsible for the evoked pain perception. Prostaglandins are not stored preformed in cells, but are synthesized and released in response to various stimuli (Leslie & Watkins, 1985). No signs of inflammatory reaction indicating prostaglandin release such as post-stimulus pain, hyperalgesia, erythema or oedema were evoked by the short laser pulses. Therefore, the analgesic effect of ibuprofen on laser-induced pain probably reflects a mechanism of action other than suppression of peripheral prostaglandin synthesis. This may be a centrally mediated action on e.g. prostaglandin release (Berge, 1986, Chen & Chapman, 1980) or a direct effect on peripheral nerve endings (Dubinsky & Schupsky, 1984; McLean & Gluckman, 1983).

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